REMARKS

Claims 1-29 are currently pending in this application. Claims 30-48 have been withdrawn; claim 29 has been cancelled without prejudice to further prosecution of the cancelled subject matter; and claims 1 and 23 have been amended. Upon entry of these amendments, claims 1-28 will be pending and under active consideration. Claims 1 and 23 are independent.

Applicants submit respectfully that the amendments presented herein are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. Claims 1 and 23 have been amended herein to recite "at least three coaxially arranged" hollow fibers; "at least three" compartments, comprising: a first compartment defined by the inner side of the innermost hollow fiber; and at least "two" compartments defined by a respective annular space between adjacent fibers of the at least three coaxial hollow fibers. The amendments are supported fully by the claims, figures, and throughout the specification as originally filed. In particular, the amendment to claim 1 finds support, at least, at Figure 1 and page 16, lines 8-12.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 1-4, 8-13, 18, 21, and 29 remain rejected under 35 U.S.C. § 102(b) over U.S. Patent No. 5,015,585 to Robinson (hereinafter, "Robinson"). Briefly, the Office Action states that Robinson discloses a bioreactor with a housing having nutrient inlets and outlets that allow nutrient solutions to pass therethrough and an array of coaxial semipermeable fibers defining compartments within the innermost fiber, between the innermost fiber and the outermost fiber, and outside the outermost fiber. The Office Action further alleges that nutrient solutions serve as an extracellular matrix by providing nutrients required for cell homeostasis and may contain oxygen. With regard to the Applicants assertion that the instant invention supplies oxygen through a gas introduction means, without requiring dissolution in liquid media prior to its introduction into the housing, the Office Action states that Robinson "discloses an inlet and

outlet though with [sic] oxygen, which is a gas, flows, thereby anticipating applicants' claims drawn to [same]." Applicants respectfully traverse the § 102(b) rejection.

Independent claims 1 and 23, as amended, are directed, in relevant part, to a bioreactor, comprising a housing having an inner side further comprising a gas introduction means integral to the housing and a gas expiration means integral to the housing and a plurality of modules each comprising at least three coaxial fibers. In other words, bioreactors of the instant invention comprise, at least, (1) four compartments (one defined by the inside of the innermost fiber, two defined by the annular space between three adjacent fibers, and another "outermost" defined by the space within the inner side of the housing and the outermost fiber) and (2) a gas introduction/expiration means integral to the housing.

The addition of a fourth compartment over the teachings of Robinson, alone, materially distinguishes the claimed invention over the prior art. A four-compartment configuration allows, *inter alia*, incubating co-culture systems in a bioreactor. For example, one possible embodiment of the instant invention includes (from the innermost compartment outward): (1) a media compartment, (2) a cell type 1 compartment, (3) a cell type 2 and/or media compartment, and (4) a gas (*e.g.*, oxygen) compartment.

In addition to the inclusion of a fourth, "outermost compartment," said compartment comprises a housing having a gas introduction means integral to the housing; and a gas expiration means integral to the housing. This feature enables the outermost compartment of the instant invention to be dedicated solely to gaseous, integral aeration, defined as a consistent and even distribution of gas coaxial to length of hollow fibers. (See page 14, lines 23-34, page 20, lines 14-36, and Response dated July 11, 2003, for a discussion on "integral" versus "serial" aeration.) Thus, for example, a compartment housing cells could be "sandwiched" between two media streams, one of which could be integrally oxygenated so as to cause a radial oxygen gradient across the cell compartment.[1]

In significant contrast, the Robinson device does not provide for any compartment that may be *dedicated* to gaseous, integral aeration. As a matter of fact, Robinson distinguishes its invention from the prior art in that its bioreactors deliver *liquid* nutrients to the cells therein from

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[1] Alternatively, gas introduction and expiration means allow introduction and expiration of gaseous nutrient through the "innermost" compartment.

all sides. Indeed, "[t]he method [of Robinson] includes the convective passage of *fluidized* nutrients ...between the hollow fibers." Col. 3, lines 1-4. Lest there be any doubt that Robinson did not intend to define a gas as a fluid, the specification emphasizes that the "the prior art bioreactors have only been able to supply *gaseous* nutrients from one side and *fluidized* nutrients from the other. The situation of having *fluidized* nutrients from both sides has not been successfully achieved." (Col. 2, lines 15-18, emphasis added). Thus, where the Office Action refers to the nutrient, oxygen, disclosed by Robinson, Applicants respectfully submit that Robinson refers to oxygen gas dissolved in fluidized nutrients. Any other interpretation would not be in keeping with the disclosure and description in Robinson.

For at least these reasons, Applicants submit that the claimed invention is not anticipated by Robinson, and respectfully request withdrawal of the § 102(b) rejections.

A. U.S. Patent No. 4,440, 853

Applicants wish to direct the Examiner's attention to U.S. Patent No. 5,015,585 to Michaels *et al.* (hereinafter, "Michaels") and distinguish the instant claimed invention therefrom.

Michaels discloses reactors of the following description:

> "The microorganisms are inoculated into the *fluid* in the space *surrounding the hollow fibers*, while a nutrient medium is directed to the lumen of the hollow fibers. The nutrients and substrates pass, by flowing or diffusing into the pores of the hollow fiber wall containing the microorganisms, while the microbiological products flow or diffuse back into the lumen and into the interfiber spaces. In this way, nutrient continuously washes the microorganisms in the pores and products are removed from the pores to prevent inhibition of the microorganism metabolism." (Col. 2, paragraph 4, emphasis added.)

With respect to the embodiment depicted in FIG. 3, the specification further recites, "a gas inlet conduit connects to [a] gas manifold which distributes the gas evenly about the periphery of the housing." In other words, the reactors of Michaels (*e.g.*, FIG. 3) comprise a shell comprising a plurality of hollow, porous fibers held in position and provided access to media entrance and exit chambers. (Col. 5, lines 66-68.) These fibers are bathed in fluid, both "in the space surrounding...[and]...into the lumen of the hollow fibers." According to the description above, the microorganisms take residence "in the hollow fiber wall, while the microbial products flow ...back into the lumen."

The reactors of Michaels, however, do not teach or suggest any compartment, such as the outermost compartment of the instant invention, that can provide exclusively a gaseous nutrient coaxial and, thereby, on all faces of the hollow fibers. As a first matter, Applicants note that Michaels describes a 2-compartment reactor composed of the lumen compartment (inside the porous hollow fibers) and the "interfiber space." The liquid nutrient medium is introduced into the lumen at one end of the porous hollow fibers and allowed to permeate to the outside of the porous hollow fibers, filling this "interfiber space" with liquid media. (The liquid media re-enters the porous hollow fibers before exiting at the opposite end of the porous hollow fibers and out of the bioreactor, as described.) Accordingly, the vessel is filled with fluid, leaving no separate compartment for gaseous nutrients *only* as claimed in the instant application.

Alternatively, it is arguably possible that pressurized oxygen could be introduced (*e.g.*, through the gas inlet conduit) into the "interfiber space" of a Michaels reactor. Even in this instance, no compartment, devoid of liquid nutrients, is provided by the teachings or suggestions of Michaels. At best, introduction of a gas into the "interfiber space" of a Michaels reactor would arguably provide both gas and liquid in the "interfiber space." In marked contrast, the instant invention provides for an outermost compartment defined by a space that runs along the inner side of the housing and the coaxially arranged hollow fibers (within the plurality of modules). This configuration allows a compartment, solely containing gas, to provide integral aeration of liquid media at almost all points along a flow path for the plurality of modules.

Applicants' four-separate-compartment design makes this "integral aeration" possible, allowing gas to run the length of the bioreactor either through the outermost compartment (or, in the alternative, the innermost compartment). Therefore, in light of the above amendments, cancellation of claim 29, and remarks, Applicants submit respectfully that the rejection to claims 1-4, 8-13, 18, and 21 under 35 U.S.C. § 102(b) has been overcome and kindly request that the same rejections be withdrawn.

II. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The rejections over Robinson alone or in view of Naughton

Claims 5-7, 14, 19-20, and 23-27 stand rejected under 35 U.S.C. § 103(a) over Robinson either alone or in view of U.S. Patent No. 6,218,182 to Naughton *et al.* (hereinafter,

"Naughton"). The Office Action states, in brief, that Robinson teaches all the limitations of the rejected claims with respect to the apparatus with the exception of using liver cells, the number of cells in the reactor, and the pore size of the fibers, but that these deficiencies are allegedly cured through obvious modification. With respect to claims 15, 22, and 28, the Office Action acknowledges that Robinson does not disclose treatment of a patient, but alleges that this deficiency in Robinson is cured by Naughton. Applicants traverse respectfully.

Applicants respectfully submit that the novel devices and methods of the present invention are neither taught nor suggested by Robinson, either alone or in view of Naughton. There is neither teaching nor suggestion in these references that the device include integral aeration means, such as the integral gas inlets and outlets for a fourth compartment as claimed in the present invention. As noted above, Robinson neither teaches nor suggests such integral aeration means, and the Office Action does not assert either that such integral aeration would be obvious over Robinson alone or that Naughton cures this deficiency. In fact, by teaching that the nutrient solution may be oxygenated prior to entry into device (see, for example, Robinson at Column 6, lines 16-22), Robinson arguably teaches away from an integral oxygenation system, favoring serial oxygenation. Thus, Applicants submit respectfully that, as neither Robinson alone nor the combination with Naughton cure the deficiencies of Robinson with respect to the integral aeration means and four compartments of the present invention, neither Robinson alone, nor the combination with Naughton, meets the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

Accordingly, Applicants respectfully submit that the rejection of Claims 5-7, 14-15, 19-20, and 22-28 under 35 U.S.C. § 103(a) have been overcome, and Applicants request respectfully that the rejection of Claims 5-7, 14, 19-20, and 23-27 under 35 U.S.C. § 103(a) be withdrawn.

B. The rejection over Robinson in view of Naughton in view of Stephanopoulis

Claims 16 and 17 remain rejected over Robinson in view of Naughton and further in view of U.S. Patent No. 5,510,262 to Stephanopoulis *et al.* (hereinafter, "Stephanopoulis") under 35 U.S.C. § 103(a). Briefly, the Office Action states that Robinson and Naughton teach Applicants' claimed device with the exception of aeration and perfluorocarbon coating on the microfiber growth area and that Stephanopoulis cures this deficiency. Applicants traverse respectfully.

While admitting that Robinson in view of Naughton is deficient with respect to Applicants' claimed invention, the Office Action alleges that Stephanopoulis cures those deficiencies by teaching a hollow fiber cell culture device, wherein the medium is aerated by containment in a growth medium reservoir and that perfluorocarbon may be added to the medium to increase the oxygen solubility in the growth medium. Applicants submit respectfully that Stephanopoulis in combination with Robinson and Naughton does not reach Applicants' claimed invention. Robinson, as noted above, at best teaches away from the modification of Stephanopoulis (*i.e.*, teaches away from an integral aeration system by providing a nutrient medium that is oxygenated prior to entry into the bioreactor). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). It is improper to combine references where the references teach away from their combination. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Assuming, *arguendo*, Stephanopoulis could be combined with Robinson in view of Naughton, such a combination would not cure Robinson's deficiencies. As alleged in the Office Action, Stephanopoulis teaches a hollow fiber cell culture device wherein the medium is aerated by containment in a growth medium reservoir, from which the nutrient medium is circulated into the bioreactor, and that perfluorocarbon may be added to the medium to increase the oxygen solubility in the growth medium. Applicants' claimed invention is not directed to a separate growth medium reservoir *for the aeration of the growth medium*. Instead, the aeration occurs within the bioreactor itself and occurs by diffusion rather than by injection. Furthermore, Applicants' use of perfluorocarbon occurs at the microfiber itself rather than in a separate growth medium reservoir, as in the Stephanopoulis device. Thus, Applicants submit respectfully that these aspects of the Stephanopoulis device are patentably distinct from Applicants' claimed invention and cannot cure the deficiencies of Robinson and Naughton.

Accordingly, Applicants submit respectfully that the rejection of Claims 16 and 17 under 35 U.S.C. § 103(a) has been overcome, and Applicants request respectfully that the rejection of Claims 16 and 17 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

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